



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (21) International Application Number: PCT/CA00/00165 (22) International Filing Date: 18 February 2000 (18.02.00) (30) Priority Data: 60/120,784 19 February 1999 (19.02.99) US (71) Applicant (for all designated States except US): McMASTER UNIVERSITY [CA/CA]; 1200 Main Street West, Health Science Centre, Room 3N43, Hamilton, Ontario L8N 3Z5 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): RUDNICKI, Michael, A. [CA/CA]; 14 Sherwood Rise, Dundas, Ontario L9H 4E8 (CA). SABOURIN, Luc, A. [CA/CA]; 280 South Kingsway, Toronto, Ontario M6S 3T9 (CA). (74) Agent: BERESKIN & PARR; 40 King Street West, 40th Floor, Toronto, Ontario M5H 3Y2 (CA). | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i> |
| (54) Title: A CASPASE ACTIVATED PROTEIN KINASE (57) Abstract <p>A novel Ste20-related protein kinase, called SMAK, and methods for its preparation and use are provided. Nucleic acids encoding SMAK and methods for their use in preparing SMAK as well as in preparing and identifying SMAK analogs are provided.</p> | | |



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- (21) International Application Number: PCT/CA00/00165
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60/120,784 19 February 1999 (19.02.1999) US
- (71) Applicant (for all designated States except US): McMASTER UNIVERSITY [CA/CA]; 1200 Main Street West, Health Science Centre, Room 3N43, Hamilton, Ontario L8N 3Z5 (CA).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): RUDNICKI, Michael, A. [CA/CA]; 14 Sherwood Rise, Dundas, Ontario L9H 4E8 (CA). SABOURIN, Luc, A. [CA/CA]; 280 South Kingsway, Toronto, Ontario M6S 3T9 (CA).
- (74) Agent: BERESKIN & PARR; 40 King Street West, 40th Floor, Toronto, Ontario M5H 3Y2 (CA).
- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
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(54) Title: A CASPASE ACTIVATED PROTEIN KINASE

(57) Abstract: A novel Ste20-related protein kinase, called SMAK, and methods for its preparation and use are provided. Nucleic acids encoding SMAK and methods for their use in preparing SMAK as well as in preparing and identifying SMAK analogs are provided.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N9/12 C12N15/54 C12N15/63 C12N15/11 C07K16/40
G01N33/53 A61K38/17 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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STRAND, EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | <p>DATABASE EMBL NUCLEOTIDE AND PROTEIN SEQUENCES, 17 January 1998 (1998-01-17), XP002144032 HINXTON, GB AC = AF039574. Mus musculus serine/threonine protein kinase mRNA, complete cds. Pytowski B., et al., Cellular and Molecular Biology, ImClone Systems, Inc., NY 10014, USA. abstract</p> <p style="text-align: center;">--- -/--</p> | 1,3-5, 11,13,16 |



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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | <p>WO 97 42212 A (GEN HOSPITAL CORP) 13 November 1997 (1997-11-13) Fig 1. the whole document</p> <p style="text-align: center;">---</p> | 1-28 |
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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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| A | <p>DATABASE EMBL NUCLEOTIDE AND PROTEIN SEQUENCES, 1 July 1997 (1997-07-01), XP002144039 HINXTON, GB AC = 008986. NUCLEUS AND MICROTUBULE-ASSOCIATED PROTEIN (FRAGMENT). Cricetulus longicaudatus abstract</p> | 2,3,11, 13 |
| P,X | <p>KURAMOCHI S ET AL: "MOLECULAR CLONING OF THE HUMAN GENE STK10 ENCODING LYMPHOCYTE-ORIENTED KINASE, AND COMPARITIVE CHROMOSOMAL MAPPING OF THE HUMAN MOUSE, AND RAT HOMOLOGUES" IMMUNOGENETICS, DE, SPRINGER VERLAG, BERLIN, vol. 49, no. 5, May 1999 (1999-05), pages 369-375, XP000881731 ISSN: 0093-7711 the whole document</p> | 3,4,11, 13,16 |

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| P,X | <p>DATABASE EMBL NUCLEOTIDE AND PROTEIN SEQUENCES, 1 November 1999 (1999-11-01), XP002144040 HINXTON, GB AC = Q9WU41. STE20-RELATED KINASE SMAK. SMAC. Mus musculus. abstract -& SABOURIN L.A. ET AL., : "Caspase 3 cleavage of the Ste20-related kinase SLK releases and activates an apoptosis-inducing kinase domain and an actin-disassembling region" MOL. CELL. BIOL., vol. 20, no. 2, January 2000 (2000-01), pages 684-696, XP000925841 the whole document</p> | 1-28 |
| P,X | <p>WO 99 29857 A (BEST JENNIFER ;VAIL BRENDA (US); ZON LEONARD I (US); AGARWAL SADHA) 17 June 1999 (1999-06-17) SEQ.ID.N.8 the whole document</p> | 1-28 |
| P,X | <p>WO 99 32637 A (ZENECA LTD) 1 July 1999 (1999-07-01) SEQ.ID.N.4 abstract page 7-54</p> | 1-28 |
| P,X | <p>WO 99 53036 A (SUGEN INC ;WHYTE DAVID (US); PLOWMAN GREGORY (US); MARTINEZ RICARD) 21 October 1999 (1999-10-21) SEQ.ID.N. 25,84,92,107. abstract page 3, line 5-24; examples 1-7</p> | 1-28 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N9/12 C12N15/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| Y | WO 97 42212 A (GEN HOSPITAL CORP) 13 November 1997 (1997-11-13) page 2, line 18 -page 9, line 12 page 10, line 9 -page 11, line 23 page 17, line 11 -page 19, line 13 All inventions --- | 1-15, 21-24, 29-32 |
| Y | BUCHER ET AL: "A flexible motif search technique based on generalized profiles" COMPUTERS AND CHEMISTRY, GB, PERGAMON PRESS, OXFORD, vol. 20, no. 1, 1996, pages 3-23, XP002107535 ISSN: 0097-8485 the whole document All inventions --- -/- | 1-15, 21-24, 29-32 |

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Date of the actual completion of the international search

8 March 2000

Date of mailing of the international search report

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Sprinks, M

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| P,X | WO 99 15635 A (ZENECA LTD) 1 April 1999 (1999-04-01) page 6, line 16 -page 8, line 13; claims 1-19; figures 1-10 Invention 1 --- | 1-15, 21-24, 29-32 |
| E | WO 99 32637 A (ZENECA LTD) 1 July 1999 (1999-07-01) page 7, line 3 -page 9, line 24; claims 1-19; figures 1-16 Invention 1 --- | 1-15, 21-24, 29-32 |
| P,X | WO 99 07854 A (MIAO NINGNING ;ONTOGENY INC (US); PANG KEVIN (US); BARKER DOUGLAS) 18 February 1999 (1999-02-18) claims 1-44; table 1 Invention 2 - see SEQ ID NO:5/6 Invention 3 - see SEQ ID NO:7/8/9 Invention 6 - see SEQ ID NO:7/8/9 --- | 1-15, 21-24, 29-32 21-24, 29-32 |
| P,Y | | |
| P,X | DATABASE EMBL [Online] ID: AF099989, 11 November 1998 (1998-11-11) JOHNSTON ET AL.: "SPAK: a novel Ste-20 related kinase expressed in the pancreas" XP002132350 abstract Invention 2 --- | 1-15 |
| P,Y | | 21-24, 29-32 |
| X | DATABASE EMBL [Online] ID: AF017635, 23 September 1997 (1997-09-23) BAYTEL ET AL.: "Homo sapiens DCHT mRNA, complete cds" XP002132351 abstract Invention 2 - clearly encodes a kinase --- | 1-15 |
| Y | | 21-24, 29-32 |
| X | DATABASE EMBL [Online] ID: MMAA20708, 21 November 1996 (1996-11-21) MARRA ET AL.: "mp54a01.r1 Soares 2NbMT Mus musculus cDNA clone 573000 5'" XP002132352 abstract Inventions 4 and 5 - no function indicated --- -/-- | 1-9 |

INTERNATIONAL SEARCH REPORT

Interr. Application No.
PCT/US 99/08150

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | <p>DATABASE EMBL [Online] ID: HS130B11B, 25 August 1995 (1995-08-25) FUJIWARA ET AL.: "Human fetal brain cDNA 5'-end GEN-130B11" XP002132353 abstract Invention 4 - no function indicated</p> | 1-9 |
| X | <p>DATABASE EMBL [Online] ID: AA766905, 30 January 1998 (1998-01-30) NCI-CGAP: "...Homo sapiens cDNA clone Image:1301771 similar to TR:Q42341 Q42341 SERINE-THREONINE PROTEIN KINASE" XP002132354 abstract</p> | 1-15 |
| Y | <p>Invention 6 - encoded function indicated</p> | 21-24, 29-32 |
| X | <p>SU ET AL.: "NIK is a new Ste20-related kinase that binds NCK and MEKK1 and activates the SAPK/JNK cascade via a conserved regulatory domain" THE EMBO JOURNAL, vol. 16, no. 6, 1997, pages 1279-1290, XP002132378 abstract; figure 1 Invention 7 - identical to residues 1-47, essentially identical from 1-495 and 625-1239 (end)</p> | 1-14,16, 21-24 |
| Y | <p>DATABASE EMBL [Online] ID: AB011123, 10 April 1998 (1998-04-10) OHARA ET AL.: "Homo sapiens mRNA for KIAA0551 protein, partial cds" XP002132377 abstract</p> | 29-32 |
| Y | <p>Invention 8 - almost 100% identical to residues 8-410 and 415-1297 (end) Invention 9 - shows significant sequence similarity</p> | 1-14,16 |
| X | <p>DATABASE EMBL [Online] ID: AA865818, 16 March 1998 (1998-03-16) NCI-CGAP: "...Homo sapiens cDNA clone IMAGE:1456752 3' similar to TR:P97820 P97820 NIK..." XP002132508 abstract</p> | 21-24, 29-32 |
| Y | <p>Invention 10 - encoded function indicated (similar to NIK, a known protein kinase)</p> | 21-24, 29-32 |

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/08150

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|--|-----------------------------|
| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | <p>DATABASE EMBL [Online] ID: HS571200, 15 September 1995 (1995-09-15) HILLIER ET AL.: "yr32h11.r1 Homo sapiens cDNA clone 207045 5'" XP002132509 abstract Invention 10 - no function indicated</p> | 1-9 |
| X | <p>DATABASE EMBL [Online] ID: HS1254577, 13 June 1997 (1997-06-13) HILLIER ET AL.: "...Homo sapiens cDNA clone 796310 5' similar to WP:ZC504.4 CE02384 SERINE/THREONINE PROTEIN KINASE" XP002132510 abstract</p> | 1-14,16 |
| Y | <p>Invention 10 - encoded function indicated</p> | 21-24, 29-32 |
| X | <p>DIENER ET AL.: "Activation of the c-Jun N-terminal kinase pathway by a novel protein kinase related to human germinal center kinase" PROC. NATL. ACAD. SCI. USA, vol. 94, September 1997 (1997-09), pages 9687-9692, XP002132504 abstract; figures 1-7 Invention 11 - GLK is identical to residues 13-391 and 393-894 (end) of KHS2</p> | 1-14,17, 21-24 |
| Y | <p>WO 99 02699 A (CADUS PHARMACEUTICAL CORP) 21 January 1999 (1999-01-21) abstract; figure 2 Invention 12</p> | 29-32 |
| P,X | <p>WO 99 02699 A (CADUS PHARMACEUTICAL CORP) 21 January 1999 (1999-01-21) abstract; figure 2 Invention 12</p> | 1-14,18, 21-24, 29-32 |
| X | <p>DATABASE EMBL [Online] ID: AA885355, 30 March 1998 (1998-03-30) NCI-CGAP: "...Homo sapiens cDNA clone IMAGE:1460315 3' similar to WP:T17E9.1 CE01405" XP002132511 abstract Invention 12 - no function indicated</p> | 1-9 |
| X | <p>DATABASE EMBL [Online] ID: AA576724, 11 September 1997 (1997-09-11) NCI-CGAP: "...Homo sapiens cDNA clone IMAGE:1074607" XP002132512 abstract Invention 12 - no function indicated</p> | 1-9 |
| | -/-- | |

INTERNATIONAL SEARCH REPORT

Intern Application No

PCT/US 99/08150

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | <p>DATABASE EMBL [Online] ID: MM1266197, 22 June 1997 (1997-06-22) MARRA ET AL.: "...Mus musculus cDNA clone 805425 5' similar to WP:T17E9.1 CE01405" XP002132513 abstract Invention 13 - no function indicated</p> <p>---</p> | 1-9 |
| P,X | <p>HUTCHISON M: "Isolation of TA01, a protein kinase that activates MEKs in stress-activated protein kinase cascades" JOURNAL OF BIOLOGICAL CHEMISTRY, US, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 273, no. 44, 30 October 1998 (1998-10-30), pages 28625-28632-28632, XP002114118 ISSN: 0021-9258 abstract; figures 1-6 Invention 13 - TA01 is essentially identical to SULU3</p> <p>---</p> | 1-14, 18, 21-24 |
| Y | <p>KURAMOCHI ET AL.: "LOK is a novel mouse STE20-like protein kinase that is expressed predominantly in lymphocytes" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 36, 5 September 1997 (1997-09-05), pages 22679-22684, XP002132505 abstract; figures 1-6 Invention 14 - LOK is essentially identical to (probably the mouse homologue of) GEK2 - identical at amino acid positions 1-33</p> <p>---</p> | 29-32 |
| X | <p>DATABASE EMBL [Online] ID: HS1259479, 20 June 1997 (1997-06-20) NCI-CGAP: "...Homo sapiens cDNA clone IMAGE:814858 3' similar to TR:G881958 G881958 MESS1" XP002132515 abstract</p> <p>---</p> | 1-14, 19, 21-24 |
| Y | <p>Invention 14 - encoded function indicated (MESS1 is a protein kinase of the prior art)</p> <p>---</p> <p>-/--</p> | 21-24, 29-32 |

INTERNATIONAL SEARCH REPORT

Form: International Application No

PCT/US 99/08150

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------------------|
| X | DATABASE EMBL [Online] ID: HS1254308, 16 June 1997 (1997-06-16) NCI-CGAP: "...Homo sapiens cDNA clone IMAGE:814858 5' similar to WP:T19A5.2 CE07510 SERINE.THREONINE KINASE" XP002132516 | 1-14,19 |
| Y | abstract | 21-24, 29-32 |
| | Invention 14 - encoded function indicated | |
| P,X | --- DATABASE EMBL [Online] ID: AB015718, 14 December 1998 (1998-12-14) KURAMOCHI ET AL.: "Homo sapiens lok mRNA for protein kinase, complete cds" XP002132514 | 1-14,19, 21-24 |
| P,Y | abstract Invention 14 - STK10 is identical to GEK2 at all but one amino acid positions | 29-32 |
| X | --- DATABASE EMBL [Online] ID: AA634299, 31 October 1997 (1997-10-31) HILLIER ET AL.: "...Homo sapiens cDNA clone 743770 3'" XP002132517 abstract Invention 15 - no function indicated | 1-9 |
| P,X | --- ABO ET AL.: "PAK4, a novel effector for Cdc42Hs, is implicated in the reorganization of the actin cytoskeleton and in the formation of filopodia" THE EMBO JOURNAL, vol. 17, no. 22, 16 November 1998 (1998-11-16), pages 6527-6540, XP002132507 | 1-14, 20-24 |
| P,Y A | abstract; figures 1-8 "A" for invention 15 - the name "PAK4" has been given to different proteins "PX", "PY" and "A" for invention 16 - "PAK5" of the present application is identical to "PAK4" of this document. ----- | 29-32 1-14, 20-24, 29-32 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/08150

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 25-28
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 25-28

It is not possible to carry out a meaningful search into the state of the art on the basis of claims 25-28 because they refer to the use of "modulators" and "kinase inhibitors" which are structurally undefined and could not in any event have been functionally tested in the prior art (assuming novelty for the kinases to which they refer).

The applicant is also requested to note that additional problems during subsequent examination may also result from the formulation of said claims, which currently refer to methods of treatment of the human or animal body.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15,21-24,29-32 partially

A nucleic acid encoding a STLK2 kinase polypeptide (SEQ ID NO:5) and subject-matter relating thereto.

2. Claims: 1-15,21-24,29-32 partially

A nucleic acid encoding a STLK3 kinase polypeptide (SEQ ID NO:6) and subject-matter relating thereto.

3. Claims: 1-15,21-24,29-32 partially

A nucleic acid encoding a STLK4 kinase polypeptide (SEQ ID NO:7) and subject-matter relating thereto.

4. Claims: 1-15,21-24,29-32 partially

A nucleic acid encoding a STLK5 kinase polypeptide (SEQ ID NO:97) and subject-matter relating thereto.

5. Claims: 1-15,21-24,29-32 partially

A nucleic acid encoding a STLK6 kinase polypeptide (SEQ ID NO:99) and subject-matter relating thereto.

6. Claims: 1-15,21-24,29-32 partially

A nucleic acid encoding a STLK7 kinase polypeptide (SEQ ID NO:101) and subject-matter relating thereto.

7. Claims: 1-14,16,21-24,29-32 partially

A nucleic acid encoding a ZC1 kinase polypeptide (SEQ ID NO:13) and subject-matter relating thereto.

8. Claims: 1-14,16,21-24,29-32 partially

A nucleic acid encoding a ZC2 kinase polypeptide (SEQ ID NO:14) and subject-matter relating thereto.

9. Claims: 1-14,16,21-24,29-32 partially

A nucleic acid encoding a ZC3 kinase polypeptide (SEQ ID NO:15) and subject-matter relating thereto.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. Claims: 1-14,16,21-24,29-32 partially

A nucleic acid encoding a ZC4 kinase polypeptide (SEQ ID NO:105) and subject-matter relating thereto.

11. Claims: 1-14,21-24,29-32 partially; 17 completely

A nucleic acid encoding a KHS2 kinase polypeptide (SEQ ID NO:18) and subject-matter relating thereto.

12. Claims: 1-14,18,21-24,29-32 partially

A nucleic acid encoding a SULU1 kinase polypeptide (SEQ ID NO:22) and subject-matter relating thereto.

13. Claims: 1-14,18,21-24,29-32 partially

A nucleic acid encoding a SULU3 kinase polypeptide (SEQ ID NO:23) and subject-matter relating thereto.

14. Claims: 1-14,21-24,29-32 partially; 19 completely

A nucleic acid encoding a GEK2 kinase polypeptide (SEQ ID NO:107) and subject-matter relating thereto.

15. Claims: 1-14,20-24,29-32 partially

A nucleic acid encoding a PAK4 kinase polypeptide (SEQ ID NO:29) and subject-matter relating thereto.

16. Claims: 1-14,20-24,29-32 partially

A nucleic acid encoding a PAK5 kinase polypeptide (SEQ ID NO:103) and subject-matter relating thereto.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/US 99/08150

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
|---|---|---------------------|----------------------------|---|---------------------|
| WO 9742212 | A | 13-11-1997 | AU 3118297 | A | 26-11-1997 |
| | | | US 5830699 | A | 03-11-1998 |
| WO 9915635 | A | 01-04-1999 | AU 9172698 | A | 12-04-1999 |
| WO 9932637 | A | 01-07-1999 | AU 1676699 | A | 12-07-1999 |
| | | | US 5962265 | A | 05-10-1999 |
| WO 9907854 | A | 18-02-1999 | AU 8778698 | A | 01-03-1999 |
| WO 9902699 | A | 21-01-1999 | AU 8296698 | A | 08-02-1999 |

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|--|---|--|
| Applicant's or agent's file reference 3244-37 | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/CA 00/ 00165 | International filing date (day/month/year) 18/02/2000 | (Earliest) Priority Date (day/month/year) 19/02/1999 |
| Applicant McMASTER UNIVERSITY et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item:

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PC 00/00165

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N9/12 C12N15/54 C12N15/63 C12N15/11 C07K16/40
G01N33/53 A61K38/17 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

STRAND, EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | <p>DATABASE EMBL NUCLEOTIDE AND PROTEIN SEQUENCES, 17 January 1998 (1998-01-17), XP002144032 HINXTON, GB AC = AF039574. Mus musculus serine/threonine protein kinase mRNA, complete cds. Pytowski B., et al., Cellular and Molecular Biology, ImClone Systems, Inc., NY 10014, USA. abstract</p> <p>---</p> <p>-/--</p> | 1, 3-5, 11, 13, 16 |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

11 August 2000

Date of mailing of the international search report

07/09/2000

Name and mailing address of the ISA

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Mateo Rosell, A.M.

INTERNATIONAL SEARCH REPORT

International Application No

PC 00/00165

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | <p>DATABASE EMBL NUCLEOTIDE AND PROTEIN SEQUENCES, 22 May 1997 (1997-05-22), XP002144033 HINXTON, GB AC = AB003357. Rattus norvegicus mRNA for protein kinase, complete cds.; SK2. abstract</p> <p>---</p> | 1,3-5, 11,13,16 |
| X | <p>DATABASE EMBL NUCLEOTIDE AND PROTEIN SEQUENCES, 18 April 1997 (1997-04-18), XP002144034 HINXTON, GB AC = AB002804. Homo sapiens mRNA for hSLK, complete cds. abstract & YAMADA E., ET AL., : "Molecular cloning and characterization of a novel human STE20-like kinase, hSLK" BIOCHIM. BIOPHYS. ACTA, vol. 1495, 2000, page 250-262</p> <p>---</p> | 1,3-5, 11,13,16 |
| X | <p>DATABASE EMBL NUCLEOTIDE AND PROTEIN SEQUENCES, 30 March 1998 (1998-03-30), XP002144054 HINXTON, GB AC = AA880588. vw92e05.r1 Stratagene mouse skin (#937313) Mus musculus cDNA clone IMAGE:1262432 5' similar to TR:000211 000211 HSLK. ;, mRNA sequence. EST. abstract</p> <p>---</p> | 1,3-5, 11,13,16 |
| X | <p>DATABASE EMBL NUCLEOTIDE AND PROTEIN SEQUENCES, 15 January 1997 (1997-01-15), XP002144055 HINXTON, GB AC = AA153777. mr85a04.r1 Stratagene mouse heart (#937316) Mus musculus cDNA clone IMAGE:604206 5' similar to TR:G881958 G881958 MESS1. ;, mRNA sequence. EST. abstract</p> <p>---</p> | 1,3-5, 11,13,16 |
| X | <p>DATABASE EMBL NUCLEOTIDE AND PROTEIN SEQUENCES, 1 February 1997 (1997-02-01), XP002144035 HINXTON, GB AC = Q92603. KIAA0204 PROTEIN. Homo sapiens. abstract</p> <p>---</p> | 2,11,13 |
| A | <p>WO 97 42212 A (GEN HOSPITAL CORP) 13 November 1997 (1997-11-13) Fig 1. the whole document</p> <p>---</p> | 1-28 |

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INTERNATIONAL SEARCH REPORT

International Application No

PC 00/00165

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | <p>KURAMOCHI ET AL: "LOK is a novel mouse STE20-like protein kinase that is expressed predominantly in lymphocytes" JOURNAL OF BIOLOGICAL CHEMISTRY, US, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 272, no. 36, 5 September 1997 (1997-09-05), pages 22679-22684-22684, XP002132505 ISSN: 0021-9258 cited in the application the whole document</p> <p>---</p> | 1-28 |
| A | <p>CREASY C L ET AL: "Cloning and characterization of a member of the MST subfamily of Ste20-like kinases" GENE, NL, ELSEVIER BIOMEDICAL PRESS. AMSTERDAM, vol. 167, no. 1, 1995, pages 303-306, XP004043060 ISSN: 0378-1119 cited in the application the whole document</p> <p>---</p> | 1-11 |
| A | <p>SCHAAR D G ET AL: "THE IDENTIFICATION OF A NOVEL CDNA PREFERENTIALLY EXPRESSED IN THE OLFACTORY-LIMBIC SYSTEM OF THE ADULT RAT" BRAIN RESEARCH, NL, AMSTERDAM, vol. 721, 30 January 1996 (1996-01-30), pages 217-228, XP000881673 ISSN: 0006-8993 cited in the application abstract; figure 1 page 225, left-hand column, last paragraph -page 227, left-hand column, paragraph 1</p> <p>---</p> | 2, 13 |
| A | <p>GRAVES JONATHAN D ET AL: "Caspase-mediated activation and induction of apoptosis by the mammalian Ste20-like kinase Mst1." EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL, vol. 17, no. 8, 15 April 1998 (1998-04-15), pages 2224-2234, XP002144036 ISSN: 0261-4189 cited in the application the whole document</p> <p>---</p> <p style="text-align: center;">-/--</p> | 1, 3, 11, 13, 16 |

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/A 00/00165

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | <p>SCHINKMANN ET AL: "Cloning and characterization of a human STE20-like protein kinase with unusual cofactor requirements"</p> <p>JOURNAL OF BIOLOGICAL CHEMISTRY, US, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 272, no. 45, 7 November 1997 (1997-11-07), pages 28695-28703, XP002086764 ISSN: 0021-9258 cited in the application figure 2</p> <p>---</p> | 1-28 |
| A | <p>SUSUMU ITOH ET AL: "Molecular cloning and characterization of a novel putative STE20-like kinase in Guinea pigs"</p> <p>ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, US, NEW YORK, US, vol. 340, no. 2, 15 April 1997 (1997-04-15), pages 201-207, XP002079735 ISSN: 0003-9861 the whole document</p> <p>---</p> | 1-28 |
| A | <p>ICHIJO HIDENORI ET AL: "Induction of apoptosis by ASK1, a mammalian MAPKKK that activates SAPK/JNK and p38 signaling pathways."</p> <p>SCIENCE (WASHINGTON D C), vol. 275, no. 5296, 1997, pages 90-94, XP000933551 ISSN: 0036-8075 cited in the application the whole document</p> <p>---</p> | 1-28 |
| A | <p>FANGER G R ET AL: "MEKKs, GCKs, MLKs, PAKs, TAKs, and tpls: upstream regulators of the c-Jun amino-terminal kinases?"</p> <p>CURRENT OPINION IN GENETICS & DEVELOPMENT, XX, CURRENT BIOLOGY LTD, vol. 7, February 1997 (1997-02), pages 67-74, XP000867511 ISSN: 0959-437X cited in the application Figure 1 the whole document</p> <p>---</p> <p style="text-align: center;">-/--</p> | 1 |

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INTERNATIONAL SEARCH REPORT

International Application No

P A 00/00165

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | NOBES CATHERINE D ET AL: "Rho, Rac, and Cdc42 GTPases Regulate the Assembly of Multimolecular Focal Complexes Associated with Actin Stress Fibers, Lamellipodia, and Filopodia." CELL, vol. 81, no. 1, 1995, pages 53-62, XP000929500 ISSN: 0092-8674 cited in the application the whole document | 1 |
| A | --- MANSEER EDWARD ET AL: "Expression of constitutively active alpha-PAK reveals effects of the kinase on actin and focal complexes." MOLECULAR AND CELLULAR BIOLOGY, vol. 17, no. 3, 1997, pages 1129-1143, XP002144038 ISSN: 0270-7306 cited in the application the whole document | 1 |
| A | --- DATABASE EMBL NUCLEOTIDE AND PROTEIN SEQUENCES, 1 July 1997 (1997-07-01), XP002144039 HINXTON, GB AC = 008986. NUCLEUS AND MICROTUBULE-ASSOCIATED PROTEIN (FRAGMENT). Cricetulus longicaudatus abstract | 2,3,11, 13 |
| P,X | --- KURAMOCHI S ET AL: "MOLECULAR CLONING OF THE HUMAN GENE STK10 ENCODING LYMPHOCYTE-ORIENTED KINASE, AND COMPARITIVE CHROMOSOMAL MAPPING OF THE HUMAN MOUSE, AND RAT HOMOLOGUES" IMMUNOGENETICS, DE, SPRINGER VERLAG, BERLIN, vol. 49, no. 5, May 1999 (1999-05), pages 369-375, XP000881731 ISSN: 0093-7711 the whole document --- -/-- | 3,4,11, 13,16 |

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INTERNATIONAL SEARCH REPORT

International Application No

P A 00/00165

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| P,X | <p>DATABASE EMBL NUCLEOTIDE AND PROTEIN SEQUENCES, 1 November 1999 (1999-11-01), XP002144040 HINXTON, GB AC = Q9WU41. STE20-RELATED KINASE SMAK. SMAK. Mus musculus. abstract -& SABOURIN L.A. ET AL., : "Caspase 3 cleavage of the Ste20-related kinase SLK releases and activates an apoptosis-inducing kinase domain and an actin-disassembling region" MOL. CELL. BIOL., vol. 20, no. 2, January 2000 (2000-01), pages 684-696, XP000925841 the whole document</p> | 1-28 |
| P,X | <p>WO 99 29857 A (BEST JENNIFER ;VAIL BRENDA (US); ZON LEONARD I (US); AGARWAL SADHA) 17 June 1999 (1999-06-17) SEQ.ID.N.8 the whole document</p> | 1-28 |
| P,X | <p>WO 99 32637 A (ZENECA LTD) 1 July 1999 (1999-07-01) SEQ.ID.N.4 abstract page 7-54</p> | 1-28 |
| P,X | <p>WO 99 53036 A (SUGEN INC ;WHYTE DAVID (US); PLOWMAN GREGORY (US); MARTINEZ RICARD) 21 October 1999 (1999-10-21) SEQ.ID.N. 25,84,92,107. abstract page 3, line 5-24; examples 1-7</p> | 1-28 |

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

P A 00/00165

| Patent document cited in search report | | Publication date | | Patent family member(s) | | Publication date |
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INTERNATIONAL SEARCH REPORT

Intern: al Application No

PCT/US 99/08150

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N9/12 C12N15/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|--------------------------|
| Y | WO 97 42212 A (GEN HOSPITAL CORP) 13 November 1997 (1997-11-13) page 2, line 18 -page 9, line 12 page 10, line 9 -page 11, line 23 page 17, line 11 -page 19, line 13 All inventions | 1-15, 21-24, 29-32 |
| Y | BUCHER ET AL: "A flexible motif search technique based on generalized profiles" COMPUTERS AND CHEMISTRY,GB,PERGAMON PRESS, OXFORD, vol. 20, no. 1, 1996, pages 3-23, XP002107535 ISSN: 0097-8485 the whole document All inventions | 1-15, 21-24, 29-32 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

8 March 2000

Date of mailing of the international search report

17. 03. 00

Name and mailing address of the ISA

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Authorized officer

Sprinks, M

INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/US 99/08150

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|---|
| P,X | WO 99 15635 A (ZENECA LTD) 1 April 1999 (1999-04-01) page 6, line 16 -page 8, line 13; claims 1-19; figures 1-10 Invention 1 --- | 1-15, 21-24, 29-32 |
| E | WO 99 32637 A (ZENECA LTD) 1 July 1999 (1999-07-01) page 7, line 3 -page 9, line 24; claims 1-19; figures 1-16 Invention 1 --- | 1-15, 21-24, 29-32 |
| P,X | WO 99 07854 A (MIAO NINGNING ;ONTOGENY INC (US); PANG KEVIN (US); BARKER DOUGLAS) 18 February 1999 (1999-02-18) claims 1-44; table 1 --- | 1-15, 21-24, 29-32 21-24, 29-32 |
| P,Y | Invention 2 - see SEQ ID NO:5/6 Invention 3 - see SEQ ID NO:7/8/9 Invention 6 - see SEQ ID NO:7/8/9 --- | |
| P,X | DATABASE EMBL [Online] ID: AF099989, 11 November 1998 (1998-11-11) JOHNSTON ET AL.: "SPAK: a novel Ste-20 related kinase expressed in the pancreas" XP002132350 abstract Invention 2 --- | 1-15 |
| P,Y | DATABASE EMBL [Online] ID: AF017635, 23 September 1997 (1997-09-23) BAYTEL ET AL.: "Homo sapiens DCHT mRNA, complete cds" XP002132351 abstract Invention 2 - clearly encodes a kinase --- | 21-24, 29-32 |
| X | DATABASE EMBL [Online] ID: MAA20708, 21 November 1996 (1996-11-21) MARRA ET AL.: "mp54a01.r1 Soares 2NbMT Mus musculus cDNA clone 573000 5'" XP002132352 abstract Inventions 4 and 5 - no function indicated --- | 1-15 |
| Y | | 21-24, 29-32 |
| X | | 1-9 |
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/08150

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | <p>DATABASE EMBL [Online] ID: HS130B118, 25 August 1995 (1995-08-25) FUJIWARA ET AL.: "Human fetal brain cDNA 5'-end GEN-130B11" XP002132353 abstract Invention 4 - no function indicated</p> | 1-9 |
| X | <p>DATABASE EMBL [Online] ID: AA766905, 30 January 1998 (1998-01-30) NCI-CGAP: "...Homo sapiens cDNA clone Image:1301771 similar to TR:Q42341 Q42341 SERINE-THREONINE PROTEIN KINASE" XP002132354</p> | 1-15 |
| Y | <p>abstract Invention 6 - encoded function indicated</p> | 21-24, 29-32 |
| X | <p>SU ET AL.: "NIK is a new Ste20-related kinase that binds NCK and MEKK1 and activates the SAPK/JNK cascade via a conserved regulatory domain" THE EMBO JOURNAL, vol. 16, no. 6, 1997, pages 1279-1290, XP002132378</p> | 1-14,16, 21-24 |
| Y | <p>abstract; figure 1 Invention 7 - identical to residues 1-47, essentially identical from 1-495 and 625-1239 (end)</p> | 29-32 |
| X | <p>DATABASE EMBL [Online] ID: AB011123, 10 April 1998 (1998-04-10) OHARA ET AL.: "Homo sapiens mRNA for KIAA0551 protein, partial cds" XP002132377</p> | 1-14,16 |
| Y | <p>abstract Invention 8 - almost 100% identical to residues 8-410 and 415-1297 (end) Invention 9 - shows significant sequence similarity</p> | 21-24, 29-32 |
| X | <p>DATABASE EMBL [Online] ID: AA865818, 16 March 1998 (1998-03-16) NCI-CGAP: "...Homo sapiens cDNA clone IMAGE:1456752 3' similar to TR:P97820 P97820 NIK..." XP002132508</p> | 1-14,16 |
| Y | <p>abstract Invention 10 - encoded function indicated (similar to NIK, a known protein kinase)</p> | 21-24, 29-32 |

INTERNATIONAL SEARCH REPORT

 Internat Application No
 PCT/US 99/08150

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | DATABASE EMBL [Online] ID: HS571200, 15 September 1995 (1995-09-15) HILLIER ET AL.: "yr32h11.r1 Homo sapiens cDNA clone 207045 5'" XP002132509 abstract Invention 10 - no function indicated --- | 1-9 |
| X | DATABASE EMBL [Online] ID: HS1254577, 13 June 1997 (1997-06-13) HILLIER ET AL.: "...Homo sapiens cDNA clone 796310 5' similar to WP:ZC504.4 CE02384 SERINE/THREONINE PROTEIN KINASE" XP002132510 abstract Invention 10 - encoded function indicated --- | 1-14,16 |
| Y | DIENER ET AL.: "Activation of the c-Jun N-terminal kinase pathway by a novel protein kinase related to human germinal center kinase" PROC. NATL. ACAD. SCI. USA, vol. 94, September 1997 (1997-09), pages 9687-9692, XP002132504 abstract; figures 1-7 Invention 11 - GLK is identical to residues 13-391 and 393-894 (end) of KHS2 --- | 21-24, 29-32 |
| X | WO 99 02699 A (CADUS PHARMACEUTICAL CORP) 21 January 1999 (1999-01-21) abstract; figure 2 Invention 12 --- | 1-14,17, 21-24 |
| Y | DATABASE EMBL [Online] ID: AA885355, 30 March 1998 (1998-03-30) NCI-CGAP: "...Homo sapiens cDNA clone IMAGE:1460315 3' similar to WP:T17E9:1 CE01405" XP002132511 abstract Invention 12 - no function indicated --- | 29-32 |
| P,X | DATABASE EMBL [Online] ID: AA576724, 11 September 1997 (1997-09-11) NCI-CGAP: "...Homo sapiens cDNA clone IMAGE:1074607" XP002132512 abstract Invention 12 - no function indicated --- | 1-14,18, 21-24, 29-32 |
| X | --- --- | 1-9 |
| X | --- --- | 1-9 |

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 99/08150

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| X | DATABASE EMBL [Online] ID: MM1266197, 22 June 1997 (1997-06-22) MARRA ET AL.: "...Mus musculus cDNA clone 805425 5' similar to WP:T17E9.1 CE01405" XP002132513 abstract Invention 13 - no function indicated --- | 1-9 |
| P,X | HUTCHISON M: "Isolation of TA01, a protein kinase that activates MEKs in stress-activated protein kinase cascades" JOURNAL OF BIOLOGICAL CHEMISTRY,US,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 273, no. 44, 30 October 1998 (1998-10-30), pages 28625-28632-28632, XP002114118 ISSN: 0021-9258 abstract; figures 1-6 Invention 13 - TA01 is essentially identical to SULU3 --- | 1-14,18, 21-24 |
| Y | KURAMOCHI ET AL.: "LOK is a novel mouse STE20-like protein kinase that is expressed predominantly in lymphocytes" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 36, 5 September 1997 (1997-09-05), pages 22679-22684, XP002132505 abstract; figures 1-6 Invention 14 - LOK is essentially identical to (probably the mouse homologue of) GEK2 - identical at amino acid positions 1-33 --- | 29-32 |
| X | DATABASE EMBL [Online] ID: HS1259479, 20 June 1997 (1997-06-20) NCI-CGAP: "...Homo sapiens cDNA clone IMAGE:814858 3' similar to TR:G881958 G881958 MESS1" XP002132515 abstract Invention 14 - encoded function indicated (MESS1 is a protein kinase of the prior art) --- | 1-14,19, 21-24, 29-32 |
| Y | --- | -/-- |

INTERNATIONAL SEARCH REPORT

Intern: ...al Application No

PCT/US 99/08150

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
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| X | <p>DATABASE EMBL [Online] ID: HS1254308, 16 June 1997 (1997-06-16) NCI-CGAP: "...Homo sapiens cDNA clone IMAGE:814858 5' similar to WP:T19A5.2 CE07510 SERINE.THREONINE KINASE" XP002132516</p> | 1-14,19 |
| Y | <p>abstract</p> <p>Invention 14 - encoded function indicated</p> | 21-24, 29-32 |
| P,X | <p>--- DATABASE EMBL [Online] ID: AB015718, 14 December 1998 (1998-12-14) KURAMOCHI ET AL.: "Homo sapiens lok mRNA for protein kinase, complete cds" XP002132514</p> | 1-14,19, 21-24 |
| P,Y | <p>abstract Invention 14 - STK10 is identical to GEK2 at all but one amino acid positions</p> | 29-32 |
| X | <p>--- DATABASE EMBL [Online] ID: AA634299, 31 October 1997 (1997-10-31) HILLIER ET AL.: "...Homo sapiens cDNA clone 743770 3'" XP002132517 abstract Invention 15 - no function indicated</p> | 1-9 |
| P,X | <p>--- ABO ET AL.: "PAK4, a novel effector for Cdc42Hs, is implicated in the reorganization of the actin cytoskeleton and in the formation of filopodia" THE EMBO JOURNAL, vol. 17, no. 22, 16 November 1998 (1998-11-16), pages 6527-6540, XP002132507</p> | 1-14, 20-24 |
| P,Y A | <p>abstract; figures 1-8 "A" for invention 15 - the name "PAK4" has been given to different proteins "PX", "PY" and "A" for invention 16 - "PAK5" of the present application is identical to "PAK4" of this document.</p> | 29-32 1-14, 20-24, 29-32 |
| ----- | | |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/08150

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely

2. ☒ Claims Nos.: 25-28
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 25-28

It is not possible to carry out a meaningful search into the state of the art on the basis of claims 25-28 because they refer to the use of "modulators" and "kinase inhibitors" which are structurally undefined and could not in any event have been functionally tested in the prior art (assuming novelty for the kinases to which they refer).

The applicant is also requested to note that additional problems during subsequent examination may also result from the formulation of said claims, which currently refer to methods of treatment of the human or animal body.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15,21-24,29-32 partially

A nucleic acid encoding a STLK2 kinase polypeptide (SEQ ID NO:5) and subject-matter relating thereto.

2. Claims: 1-15,21-24,29-32 partially

A nucleic acid encoding a STLK3 kinase polypeptide (SEQ ID NO:6) and subject-matter relating thereto.

3. Claims: 1-15,21-24,29-32 partially

A nucleic acid encoding a STLK4 kinase polypeptide (SEQ ID NO:7) and subject-matter relating thereto.

4. Claims: 1-15,21-24,29-32 partially

A nucleic acid encoding a STLK5 kinase polypeptide (SEQ ID NO:97) and subject-matter relating thereto.

5. Claims: 1-15,21-24,29-32 partially

A nucleic acid encoding a STLK6 kinase polypeptide (SEQ ID NO:99) and subject-matter relating thereto.

6. Claims: 1-15,21-24,29-32 partially

A nucleic acid encoding a STLK7 kinase polypeptide (SEQ ID NO:101) and subject-matter relating thereto.

7. Claims: 1-14,16,21-24,29-32 partially

A nucleic acid encoding a ZC1 kinase polypeptide (SEQ ID NO:13) and subject-matter relating thereto.

8. Claims: 1-14,16,21-24,29-32 partially

A nucleic acid encoding a ZC2 kinase polypeptide (SEQ ID NO:14) and subject-matter relating thereto.

9. Claims: 1-14,16,21-24,29-32 partially

A nucleic acid encoding a ZC3 kinase polypeptide (SEQ ID NO:15) and subject-matter relating thereto.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. Claims: 1-14,16,21-24,29-32 partially

A nucleic acid encoding a ZC4 kinase polypeptide (SEQ ID NO:105) and subject-matter relating thereto.

11. Claims: 1-14,21-24,29-32 partially; 17 completely

A nucleic acid encoding a KHS2 kinase polypeptide (SEQ ID NO:18) and subject-matter relating thereto.

12. Claims: 1-14,18,21-24,29-32 partially

A nucleic acid encoding a SULU1 kinase polypeptide (SEQ ID NO:22) and subject-matter relating thereto.

13. Claims: 1-14,18,21-24,29-32 partially

A nucleic acid encoding a SULU3 kinase polypeptide (SEQ ID NO:23) and subject-matter relating thereto.

14. Claims: 1-14,21-24,29-32 partially; 19 completely

A nucleic acid encoding a GEK2 kinase polypeptide (SEQ ID NO:107) and subject-matter relating thereto.

15. Claims: 1-14,20-24,29-32 partially

A nucleic acid encoding a PAK4 kinase polypeptide (SEQ ID NO:29) and subject-matter relating thereto.

16. Claims: 1-14,20-24,29-32 partially

A nucleic acid encoding a PAK5 kinase polypeptide (SEQ ID NO:103) and subject-matter relating thereto.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/08150

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|------------------------------|--------------------------|
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| WO 9915635 A | 01-04-1999 | AU 9172698 A | 12-04-1999 |
| WO 9932637 A | 01-07-1999 | AU 1676699 A US 5962265 A | 12-07-1999 05-10-1999 |
| WO 9907854 A | 18-02-1999 | AU 8778698 A | 01-03-1999 |
| WO 9902699 A | 21-01-1999 | AU 8296698 A | 08-02-1999 |

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

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| Date of mailing (day/month/year) 30 October 2000 (30.10.00) | |
| International application No. PCT/CA00/00165 | Applicant's or agent's file reference 3244-37 |
| International filing date (day/month/year) 18 February 2000 (18.02.00) | Priority date (day/month/year) 19 February 1999 (19.02.99) |
| Applicant RUDNICKI, Michael, A. et al | |

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

15 September 2000 (15.09.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was



was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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